Fish oil in renal transplantation

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Summary and conclusions.

Since the introduction of the immunosuppressive drug ciclosporin A (CsA), the results of virtually all organ transplant programs have shown a tremendous improvement, as illustrated by, a prolonged graft survival, a marked reduction of serious rejection episodes, and a reduction in the number of long term steroid-induced complications. Nevertheless, these improvements have been realized at the expense of newly introduced, CsA-induced side effects. Of which the most important is its nephrotoxicity. The nephrotoxic effect of CsA is not due to excessive dose regimens, but can be observed well within the therapeutic range of this drug. It has also been established that there is a strong individual sensitivity with regard to this nephrotoxic effect of CsA. Despite this complication, the use of this drug holds ample advantages in favor of former immunosuppressive regimens. Thus, the use of CsA has now been well-established as a corner stone of the immunosuppressive protocol in most renal transplant programs.

Therefore, a lot of energy has been devoted to research, aimed at elucidating the mechanisms of CsA nephrotoxicity and at developing strategies to minimize this serious limitation of the therapeutic window of this drug.

It has now been established that a reduced renal blood flow is the primary pathogenetic event in CsA nephrotoxicity. CsA has been shown to disturb the balance between the vasoconstrictor and the vasodilator eicosanoids, which are involved in the regulation of renal blood flow, and as such in the overall performance of the kidney. Following the recognition of the CsA-induced shift towards vasoconstrictor eicosanoids, studies aimed at restoring, or intervening in, the CsA-induced changes in eicosanoid metabolism have been undertaken.

Since eicosanoids, and amongst them prostaglandins, are synthesized from polyunsaturated fatty acids (PUFA), of which, in physiological conditions, arachidonic acid predominates, there seems to be a role for dietary interventions with several other PUFA's to affect renal function in CsA-treated patients.

An increasing interest in the use of fish oil, mainly constituting of EPA (C20:5 Ω-3) and DHA (C22:6Ω-3), has recently arisen. This interest has started with the reports on a reduced incidence of cardiovascular disease in Greenland eskimo's. Extensive research on this matter revealed that a diet consisting of a high intake of fish, and more precise a high intake of EPA and DHA could be held responsible for this phenomenon. Although the mechanisms by which fish oil reduces the risk for cardiovascular disease have not been completely elucidated, a number of potential mechanisms have now been proposed. Firstly, a beneficial effect on blood lipids has

been reported under various conditions; a lowering of triglycerides has been undisputedly reported, while in some but not all, studies a slight decrease in total cholesterol or a decrease in the HDL/LDL has been reported. Secondly, analogous to arachidonic acid, EPA can function as precursor for the eicosanoid metabolism. However, the EPA-derived eicosanoids have a different physiological activity, being less platelet aggretory and more vasodilatory. It has also been shown that the dietary use of EPA results in a decrease of the erythrocyte deformability and leads to a decrease of the blood viscosity.

All these properties of EPA can contribute to a decreased incidence of cardiovascular disease. Patients with end stage renal disease often have increased blood lipid levels which contribute to an increased risk for cardiovascular disease in this group of patients. This, in combination with the effects on eicosanoid synthesis, which apart from their effect on renal function might also contribute to the immune modulatory effects of fish oil, has been the justification for the hypothesis that both renal function and the risk for cardiovascular disease could possibly benefit from dietary interventions with fish oil in CsA-treated renal transplant recipients. Indeed, in experimental conditions this has been observed; therefore, it seemed fit to investigate the effects of dietary fish oil in CsA-treated renal transplant recipients.

This thesis presents the results and the perspective of a number of these clinical studies. Chapter one consists of a brief introduction and describes the aims of the studies. In chapter two the nephrotoxic properties, the pathophysiology and the clinical management of the drug CsA are reviewed, explaining the rationale and the clinical setting for a dietary intervention with fish oil.

Chapter three deals with the effects of dietary fish oil in various conditions of chronic renal insufficiency.

Chapter four deals with the short term effects of 6 g fish oil in a relative small group of renal transplant recipients with stable renal function and on cyclosporin for at least a year. In this group of patients, the addition of fish oil to their diet resulted in an increase of the GFR and the ERPF of ± 18% , while blood pressure decreased significantly with approximately 10 mmHg. These promising results raised several questions such as whether the increase in renal function can be considered as beneficial on the long term. It has, for instance, been demonstrated that the induction of so called "hyperfiltration" as measured by a loss in renal reserve filtration capacity, might be detrimental on the long term.

This matter is addressed in chapter five, in which it is shown that the addition of fish oil did not result in a loss of renal reserve filtration capacity. On the contrary the fish oil and CsA-treated patients had a higher renal reserve filtration capacity than the placebo and CsA-treated patients. These observations lead to the conclusion that a long term detrimental effect of dietary fish oil seemed unlikely. From the data presented in chapter six it is concluded that dietary fish oil has profound effects on the course of the renal function during the recovery phase following an early postoperative acute rejection episode of the renal allograft. Although per rejection episode no difference in the amount of additional immune suppression administered could be observed, the response of the renal function on the anti-rejection therapy was significantly better and faster in the fish oil-treated patients. From these data, however, we were not able to conclude whether the beneficial effects of fish oil during an acute cellular rejection episode were due to primary- immunologically or hemodynamically induced changes.

Chapter seven deals with a study with a one year follow up. In this chapter it is demonstrated that the fish oil-treated patients had a lower blood pressure and a lower calculated renal vascular resistance as well as a higher GFR, ERPF and FF at one year after grafting. Remarkable was the observed low incidence of acute rejection episodes in the fish oil-treated patients (23%) compared to the placebo oil-treated patients (64%). This clinical observation is supported by in vivo and in vitro observations on the effects of dietary fishoil on the immune system as well as by transplantation experiments, which are all reviewed in chapter eight.

As mentioned above, patients with renal disease, and especially those receiving a renal allograft have an increased risk for the development of cardiovascular disease, this is at least partially due to the presence of a number of well-known risk factors, as also reviewed in chapter eight. Although in this thesis it can not be demonstrated that dietary supplements with fish oil reduce the risk rate for cardiovascular disease in this particular group of patients, indeed there are some data presented that affect some specific risk factors. A lower blood pressure has been observed in nearly all CsA and fish oil-treated patients compared to the control groups, as also was presented in the chapters four and seven.

Parts of chapter 3 and 8 present data on the blood lipid profile before and after fish oil administration. From these data it can be concluded that triglycerides are reduced by 30%, The decrease in blood pressure and blood lipids may possibly contribute to a future decrease in the incidence of cardiovascular disease on the long term after prolonged treatment with fish oil.

In all of the above mentioned clinical trials we did not observe any serious side effects associated with the fish oil supplementation, especially hemostatic disorders were not reported in our studies.

In summary, we observed a better renal function, a lower blood pressure, a better response of renal function to anti-rejection therapy, and, after prolonged treatment a reduced incidence of acute cellular rejection after a dietary supplementation with fish oil in CsA-treated renal transplant recipients. In addition, blood lipid profile was altered in a predominant favorable manner, while no detrimental effects attributable to fish oil ingestion were observed.

Therefore, it can be stated, that despite the necessity for extension, validation and further insight in the mechanisms involved, a dietary supplement of six grams containing 50% Ω-3 poly unsaturated fatty acids is a useful and safe adjuvant therapy for CsA-treated renal transplant recipients.